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(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventors: ASBEROM, Theodros; 525 Eagle Rock Avenue, West Orange, NJ 07052 (US). LOWE, Derek, B.; 237 North 9th Street, Kenilworth, NJ 07033 (US). GREEN, Michael, J.; 1146 Rancho Encinitas Drive, Encinitas, CA 92024 (US).

(74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

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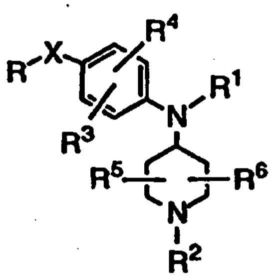
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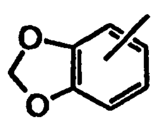
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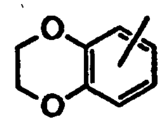
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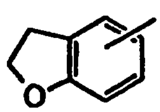
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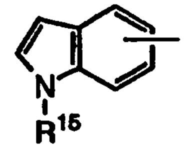
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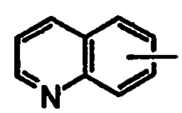
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(57) Abstract

1,4-Di-substituted piperidine muscarinic antagonists of formula (I) or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein X is a bond, -O-, -S-, -SO-, $-SO_2-$, -CO-, $-C(OR^7)_2-$, $-CH_2-O-$, $-O-CH_2-$, -CH=CH-, $-CH_2-$, $-CH(C_1-C_6\ alkyl)-$, $-C(C_1-C_6\ alkyl)_2-$, $-CONR^{17}-$, $-NR^{17}CO-$, $-SO_2NR^{17}-$ or $-NR^{17}SO_2-$; R is C_3-C_6 cycloalkyl, (a), (b), (c), (d), (e), optionally substituted phenyl or optionally substituted pyridyl; R^1 is H, -CN, $-CF_3$, alkyl, cycloalkyl, cycloalkenyl, alkenyl, $-COR^{15}$, -COO(alkyl, aryl, heteroaryl, alkylaryl or alkylheteroaryl), alkylaryl, alkylheteroaryl or $-CON(R^{13})_2$; R^2 is cycloalkyl, cycloalkenyl, t-butoxycarbonyl or optionally substituted 4-piperidinyl; R^3 and R^4 are H, halo, $-CF_3$, alkyl, alkoxy or -OH; R^5 and R^6 are H, alkyl, $-CF_3$, alkoxy, -OH, alkylcarbonyl, alkoxycarbonyl, $R^{13}CONH-$, $R^{14}OCONH-$, $R^{13}NHCONH-$ or $NH_2CONR^{13}-$; R^7 is H or alkyl, or the two R^7 groups may form $-(CH_2)_{2-4}$; R^{13} is H, alkyl, cycloalkyl, -(alkyl)$COOR^{15}$, aryl, heteroaryl, alkylaryl, alkylheteroaryl and adamantyl; R^{14} is H or alkyl; R^{15} is H, C_1-C_{20} alkyl, C_1-C_6 cycloalkyl, aryl or heteroaryl; and R^{17} is H, C_1-C_6 alkyl, aryl or heteroaryl; useful for treating cognitive disorders such as Alzheimer's disease are disclosed, as well as pharmaceutical compositions and methods of preparation. Also disclosed are combinations of compounds of formula (I) capable of enhancing ACh release with ACh'ase inhibitors.

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1,4-DI-SUSTITUTED PIPERIDINES AS MUSCARINIC ANTAGONISTS

BACKGROUND OF THE INVENTION

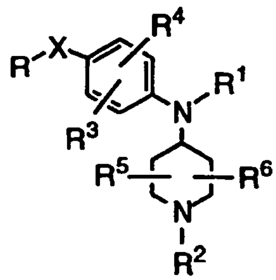
The present invention relates to 1,4-di-substituted piperidines useful in the treatment of cognitive disorders, pharmaceutical compositions containing the compounds, methods of treatment using the compounds, and to the use of said compounds in combination with acetylcholinesterase inhibitors.

Alzheimer's disease and other cognitive disorders have received much attention lately, yet treatments for these diseases have not been very successful. According to Melchiorre et al. (J. Med. Chem. (1993), 36, 3734-3737), compounds that selectively antagonize M2 muscarinic receptors, especially in relation to M1 muscarinic receptors, should possess activity against cognitive disorders. Baumgold et al. (Eur. J. of Pharmacol., 251, (1994) 315-317) disclose 3-α-chloroimperialine as a highly selective m2 muscarinic antagonist.

The present invention relates to a class of 1,4-di-substituted piperidines, some of which have m2 selectivity even higher than that of 3-α-chloroimperialine. Logemann et al (Brit. J. Pharmacol. (1961), 17, 286-296) describe certain di-N-substituted piperazines, but these are different from the inventive compounds of the present invention. Furthermore, the compounds of Logemann et al. are not disclosed to have activity against cognitive disorders.

SUMMARY OF THE INVENTION

The present invention relates to compounds according to the structural formula I,

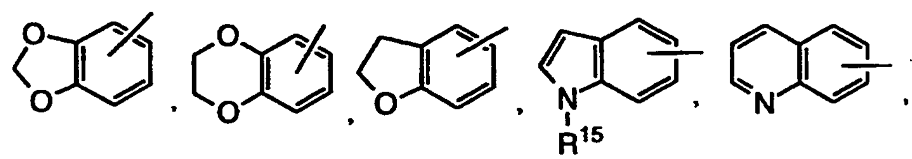


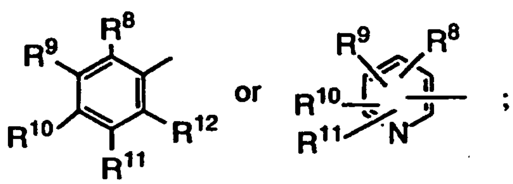
I

or an isomer, pharmaceutically acceptable salt, ester or solvate thereof, wherein

X is a bond, -O-, -S-, -SO-, $-SO_2-$, -CO-, $-C(OR^7)_2-$, $-CH_2-O-$, $-O-CH_2-$, -CH=CH-, $-CH_2-$, $-CH(C_1-C_6$ alkyl)-, $-C(C_1-C_6$ alkyl$)_2-$, $-CONR^{17}-$, $-NR^{17}CO-$, $-SO_2NR^{17}-$ or $-NR^{17}SO_2-$;

R is C_3-C_6 cycloalkyl,

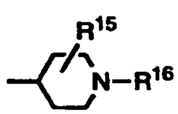




;

R^1 is H, -CN, $-CF_3$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 alkenyl, $-COR^{15}$, $-COO(C_1-C_6$ alkyl), -COO(aryl), -COO(heteroaryl), $-COO((C_1-C_6$ alkyl)aryl), $-COO((C_1-C_6$ alkyl)heteroaryl), $-(C_1-C_6$ alkyl)aryl, $-(C_1-C_6$ alkyl)heteroaryl or $-CON(R^{13})_2$;

R^2 is C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, t-butoxycarbonyl or



;

R^3 and R^4 are independently selected from the group consisting of H, halo, $-CF_3$, C_1-C_6 alkyl, C_1-C_6 alkoxy and -OH;

R^5 and R^6 are independently selected from the group consisting of H, C_1-C_6 alkyl, $-CF_3$, C_1-C_6 alkoxy, -OH, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, $R^{13}CONH-$, $R^{14}OCONH-$, $R^{13}NHCONH-$ and $NH_2CONR^{13}-$;

R^7 is independently selected from the group consisting of H and alkyl, provided that both R^7 groups are not H; or the two R^7 groups may be joined to form $-(CH_2)_p-$ wherein p is an integer of 2 to 4;

R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from the group consisting of H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, benzyloxy, benzyloxy substituted by $-NO_2$ or $-N(R^{14})$, halo C_1-C_6 alkyl, polyhalo C_1-C_6 alkyl, $-NO_2$, -CN, $-SO_2$, -OH, $-NH_2$, $-N(R^{14})_2$, -HCO, polyhalo C_1-C_6 alkoxy, acyloxy, $(C_1$-C_4 alkyl$)_3$Si-, (C_1-C_6 alkyl)SO_{0-2}, arylsulfonyl, heteroaryl-sulfonyl, acyl, (C_1-C_6 alkoxy)CO-, $-OCON(R^{14})_2$, -NHCOO-(C_1-C_6)alkyl, -NHCO-(C_1-C_6 alkyl), phenyl, hydroxy(C_1-C_6 alkyl) or morpholino;

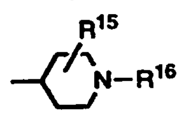
R^{13} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkyl)$COOR^{15}$, aryl, heteroaryl, -(C_1-C_6 alkyl)aryl, -(C_1-C_6 alkyl)heteroaryl and adamantyl;

R^{14} is independently selected from the group consisting of H and C_1-C_6 alkyl;

R^{15} is H, C_1-C_{20} alkyl, C_1-C_6 cycloalkyl, aryl or heteroaryl;

R^{16} is H, C_1-C_6 alkyl, $-COR^{15}$, C_1-C_6 alkoxycarbonyl, $(R^{14})_2$NCO- or $-SO_{1-2}$-R^{15}; and

R^{17} is H, C_1-C_6 alkyl, aryl or heteroaryl.

Preferred compounds of formula I are those wherein X is -SO-, $-SO_2$- or $-CH_2$-. Also preferred are compounds of formula I wherein R is R^8, R^9, R^{10}, R^{11}, R^{12}-substituted phenyl or 3,4-methylenedioxyphenyl, with 4-methoxyphenyl and 3,4-methylenedioxyphenyl being more preferred. R^3 and R^4 are preferably each hydrogen. R^1 is preferably cyano, C_1-C_6 alkyl, more preferably methyl, or C_3-C_6 alkenyl, preferably allyl. R^2 is preferably cyclohexyl or , wherein R^{16} is preferably $-COR^{15}$ wherein R^{15} is ethyl or aryl. When R^{15} is aryl, it is preferably R^8-substituted aryl, preferably R^8-substituted phenyl, especially 2-substituted phenyl wherein the substituent is methyl or halo. The R^{15} substituent attached to a ring carbon of the piperidine ring is preferably hydrogen. R^5 and R^6 are preferably independently hydrogen and $-CH_3$.

Another aspect of the invention is a pharmaceutical composition comprising a compound having structural formula I in combination with a pharmaceutically acceptable carrier.

Another aspect of the invention is the use of a compound formula I for the preparation of a pharmaceutical composition useful in the treatment of cognitive disorders and neurodegenerative diseases such as Alzheimer's disease.

Another aspect of this invention is a method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of formula I.

Another aspect of this invention is a method for treating cognitive and neurodegenerative diseases, such as Alzheimer's disease with a compound of formula I in combination with an acetylcholinesterase inhibitor.

Another aspect of this invention is a method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a combination of a compound of formula I as defined above, including stereoisomers, pharmaceutically acceptable salts, esters and solvates thereof, said compound being capable of enhancing acetylcholine (ACh) release (preferably an m2 or m4 selective muscarinic antagonist) with an acetycholinesterase (ACh'ase) inhibitor.

Another aspect of this invention is a kit comprising in separate containers in a single package pharmaceutical compounds for use in combination to treat cognitive disorders in one container a compound of formula I capable of enhancing acetylcholine release (preferably an m2 or m4 selective muscarinic antagonist) in a pharmaceutically acceptable carrier and in a second container an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier, the combined quantities being an effective amount.

DETAILED DESCRIPTION

Except where stated otherwise the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms.

Alkenyl represents a straight or branched hydrocarbon chain of 2 to 6 carbon atoms having at least one carbon-to-carbon double bond.

Cycloalkyl represents a saturated carbocyclic ring having 3 to 6 carbon atoms.

Cycloalkenyl represents a carbocyclic ring having from 3 to 6 carbon atoms and at least one carbon-to-carbon double bond in the ring.

Halo represents fluoro, chloro, bromo or iodo.

Aryl represents optionally substituted phenyl or optionally substituted naphthyl, wherein the substituents are 1 to 3 groups as defined in R^8.

Heteroaryl represents optionally substituted heteroaryl groups, wherein the substituents are 1 to 3 groups as defined in R^8, and the heteroaryl group is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, furanyl or pyrolyl.

Polyhalo represent substitution of at least 2 halo atoms to the group modified by the term "polyhalo".

Sulfonyl represents a group of the formula $-SO_2-$.

Sulfinyl represents a group of the formula -SO-.

When a variable appears more than once in the structural formula, for example R^7 when X is $-C(OR^7)_2-$, the identity of each variable appearing more than once may be independently selected from the definition for that variable.

Variables R^5 and R^6 can be attached independently to substitutable carbon atoms in the piperidinyl ring, or both variables can be attached to the same ring carbon atom.

Compounds of this invention may exist in at least two stereo configurations on the carbon to which R^5 and/or R^6 are attached, except when R^5 and R^6 are attached to the same carbon and are identical. Further stereoisomerism is present when X is SO, or $C(OR^7)_2$ (when the two R^7 groups are not the same). Also within formula I there are numerous other possibilities for stereoisomerism. All possible stereoisomers of formula I are within the scope of the invention.

Compound of formula I can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

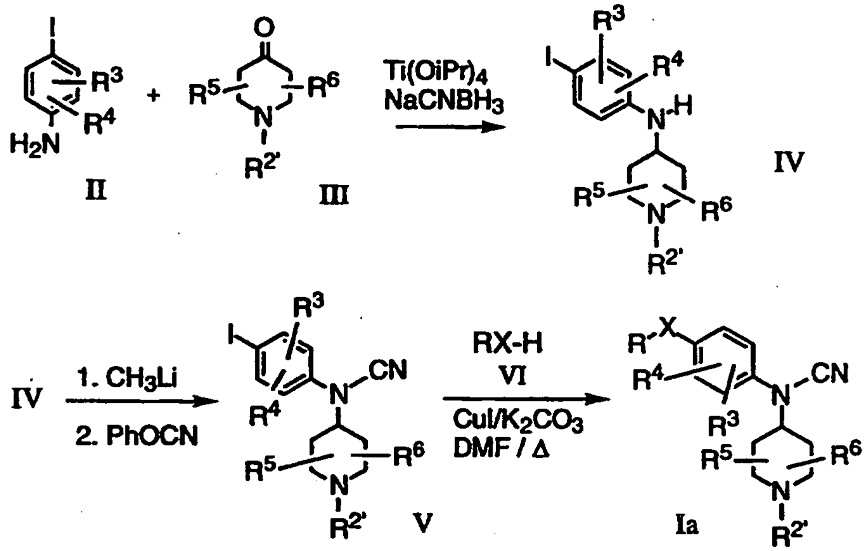
A compound of formula I may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium

hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

Compounds of formula I may be produced by processes known to those skilled in the art as exemplified by the following reaction procedures:

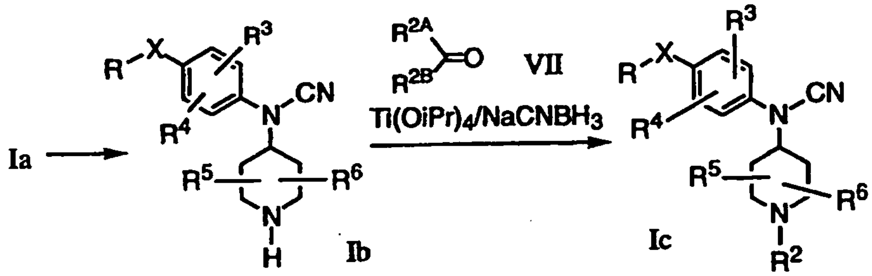
METHOD A:

Reaction Scheme A-1:



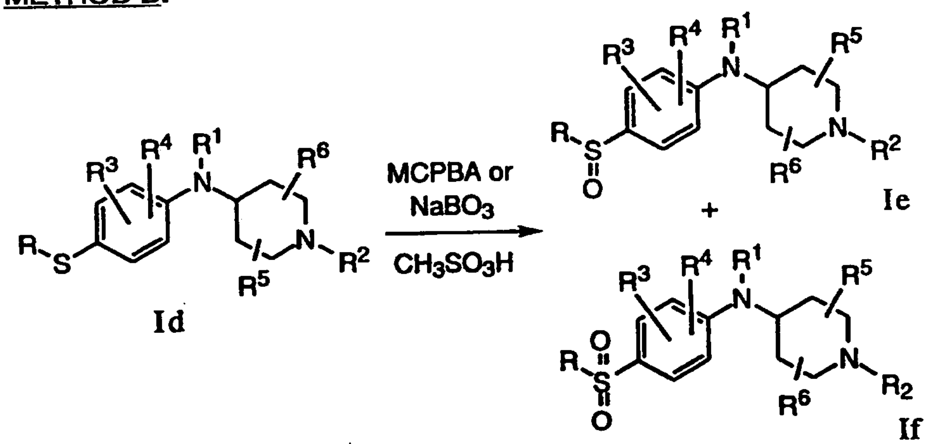
A 4-iodoaniline derivative II is reacted with a piperidone derivative III, wherein $R^{2'}$ is either R^2 as previously defined or a suitable nitrogen protecting group, in the presence of a reducing agent such as $NaCNBH_3$, preferably in the presence of a Lewis acid such as titanium isopropoxide to give aniline derivative IV. This is reacted with a strong base such as CH_3Li, followed by treatment with phenyl cyanate to give cyanoaniline V. A solution of compound V is then heated with compound VI, wherein R and X are as defined above, in the presence of a catalyst such as copper(I) iodide and a base such as K_2CO_3 to give compound Ia, wherein R^1 is cyano and the remaining variables are as defined above.

Reaction Scheme A-2:



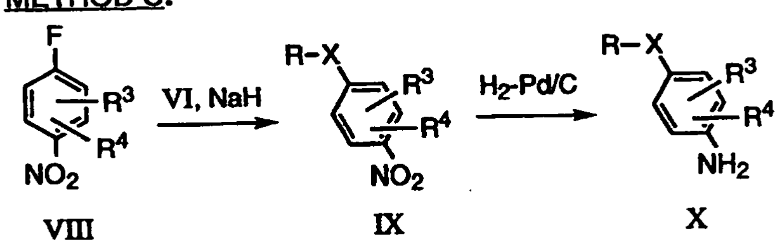
When R2' is a nitrogen protecting group, compound Ia can be transformed into compounds of formula Ib by removal of the protecting group, followed by treating Ib with a ketone VII, wherein R^{2A} and R^{2B}, together with the carbon to which they are attached, form a group R^2 as previously defined, under conditions as described in Scheme A-1 to give a compound of formula Ic, wherein R^1 is cyano and the remaining variables are as defined above.

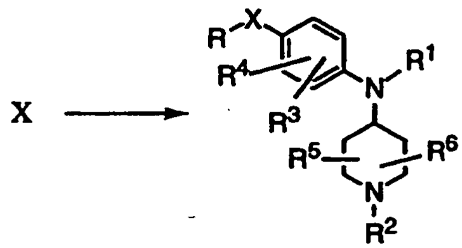
METHOD B:



Compounds of type Id, wherein X is -S- and all other variables are as previously defined, can be transformed into compounds of type Ie and If, wherein X is -S(O)- or -S(O)$_2$-, by treating Id with a suitable oxidant such as m-chloroperbenzoic acid or $NaBO_3$, preferably in the presence of an acid such as CH_3SO_3H or acetic acid.

METHOD C:

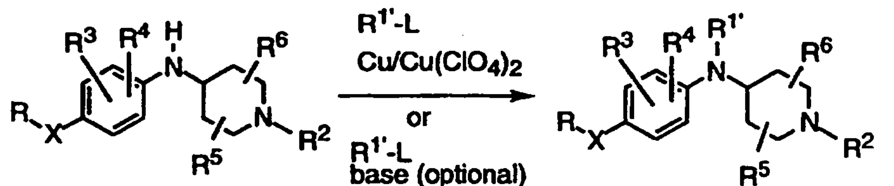




I

Compounds of formula I can also be made by treatment of a 4-fluoronitrobenzene, VIII, with a compound of formula VI, as previously defined, in the presence of a strong base such as NaH to give a substituted nitrobenzene derivative IX. The nitro group is then reduced to the aniline X under standard conditions, such as treatment with H_2 gas in the presence of a catalyst such as palladium on charcoal. Compound X can be converted to various compounds of formula I using the procedures described in Methods A, B, D and F.

METHOD D:



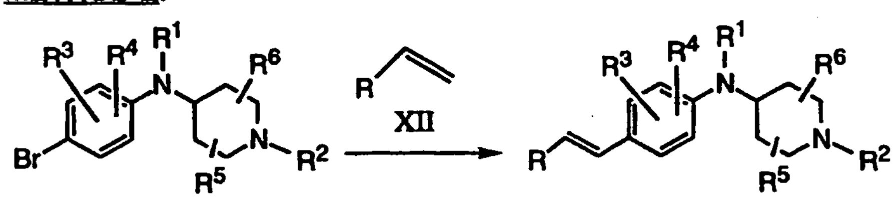
Ig Ih

Compounds of formula Ig, wherein R^1 is H and all other variables are as previously defined, can be transformed into compounds of type Ih, wherein $R^{1'}$ is alkyl or alkenyl, by:

Method D-1: Treatment of Ig with an alkenylating agent $R^{1'}$-L, wherein L is a halogen, preferably iodine or bromine, in the presence of a mixture of Cu^0 and $Cu(ClO_4)_2$; or

Method D-2: Reaction of an alkylating agent $R^{1'}$-L with Ig, where Ig is either used in excess or optionally in the presence of an added base such as CH_3Li.

METHOD E:

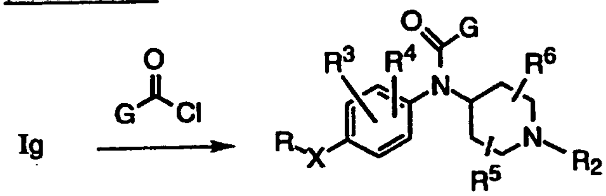


XI Ii

Compounds of type Ii, wherein X is -CH=CH-, can be prepared by treating an aryl bromide XI (prepared according to Method A-1, steps 1

and 2) with an olefin XII in the presence of a catalyst such as palladium acetate.

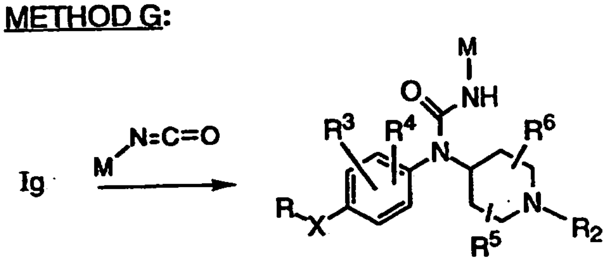
METHOD F:



Ij

Compounds of formula Ij, wherein G is alkyl, aryl, arylalkyl, alkoxy, aryloxy or arylalkoxy as defined above, can be prepared by treating compound Ig with an acylating agent G(CO)Cl (i.e., an acid chloride or a chloroformate) in a suitable solvent such as CH_2Cl_2.

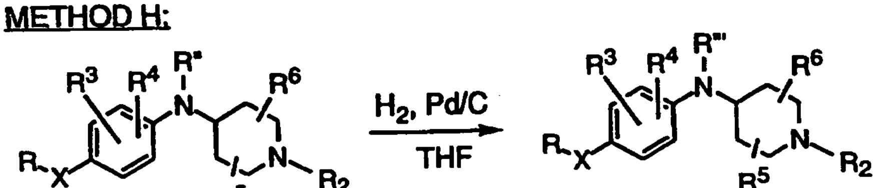
METHOD G:



Ik

Compounds of type Ik, wherein M is alkyl, aryl, or arylalkyl, can be prepared by heating compound Ig with an isocyanate M-N=C=O in a suitable solvent such as CH_3CN or toluene at a temperature sufficient to effect reaction, such as 80-150°C.

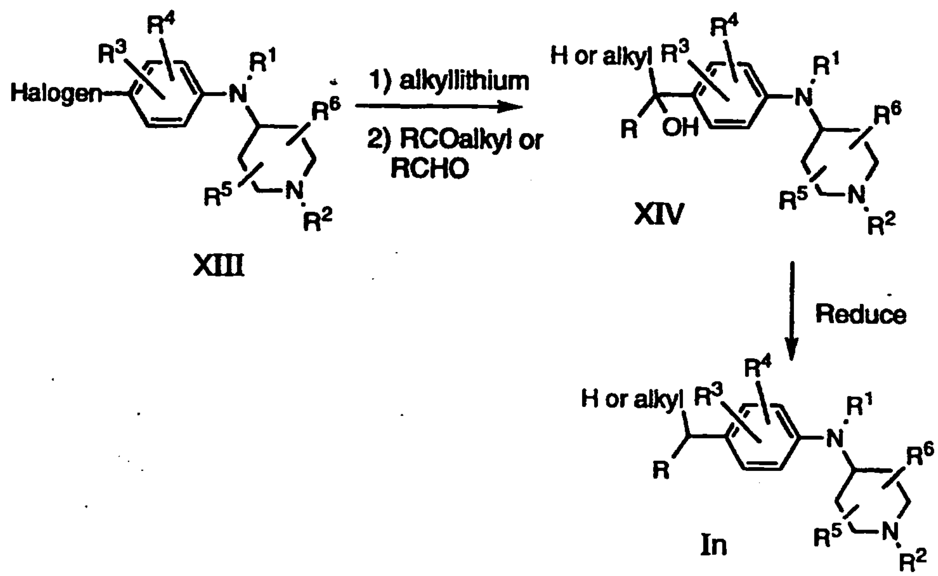
METHOD H:



Il Im

Compounds of formula Im, wherein R''' is alkyl or cycloalkyl, can be prepared by hydrogenation of the corresponding compound of formula Il, wherein R'' is alkenyl or cycloalkenyl, in the presence of a suitable catalyst such as palladium on carbon in a suitable solvent such as THF or ethanol.

METHOD I:



Compounds of type In can be prepared by treating a compound of formula XIII (prepared from compound II of reaction scheme A-1 using various methods, particularly Methods A,D, F, and/or G) with an alkyllithium reagent such as n-butyllithium or t-butyllithium in a suitable solvent such as diethyl ether or THF a low temperature, such as -78°C to 0°C. The resulting anion is treated with an aldehyde RCHO or a ketone RCO-alkyl, wherein R is as defined above, to give a carbinol of formula XIV. The carbinol is treated with a suitable reducing agent, preferably triethylsilane in the presence of a strong acid such as trifluoroacetic acid to give In.

As indicated, in the above processes it is sometimes desirable and/or necessary to protect certain groups during the reactions. Conventional protecting groups, familiar to those skilled in the art, are operable.

The above reactions may be followed if necessary or desired by one or more of the following steps; (a) removing any protective groups from the compound so produced; (b) converting the compound so-produced to a pharmaceutically acceptable salt, ester and/or solvate; (c) converting a compound in accordance with formula I so produced to another compound in accordance with formula I, and (d) isolating a compound of formula I, including separating stereoisomers of formula I.

Based on the foregoing reaction sequence, those skilled in the art will be able to select starting materials needed to produce any compound in accordance with formula I.

The compounds of formula I exhibit selective m2 and/or m4 muscarinic antagonizing activity, which has been correlated with pharmaceutical activity for treating cognitive disorders such as Alzheimers disease and senile dementia.

The compounds of formula I display pharmacological activity in test procedures designated to indicate m1, m2 and m4 muscarinic antagonist activity. The compounds are non-toxic at pharmaceutically therapeutic doses.

For preparing pharmaceutical compositions from the compounds of formula I capable of enhancing ACh release, and ACh'ase inhibitors, pharmaceutically acceptable inert carriers are admixed with the active compounds. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as dilutents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it may also be an encapsulating material.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parentertal administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit.

The invention also contemplates alternative delivery systems including, but not necessarily limited to, transdermal delivery. The transdermal compositions can take the form of creams, lotions and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active components. The unit dosage form can be a packaged preparation, the package containing

discrete quantities of preparation such as packeted tablets, capsules and powders in vials or ampules. The unit dosage form can also be a capsule, cachet or tablet itself, or it may be the appropriate number of any of these in a packaged form.

The quantity of active compound in a unit dose preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and the potency of the active ingredient and the intended treatment. This would correspond to a dose of about 0.001 to about 20 mg/kg which may be divided over 1 to 3 administrations per day. The composition may, if desired, also contain other therapeutic agents.

The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of those in the medical art. For convenience, the total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

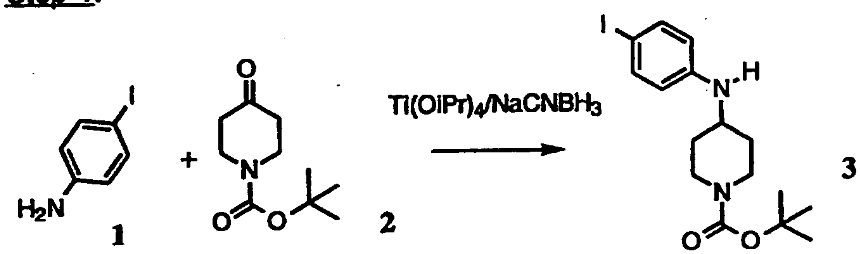
When a compound of formula I capable of enhancing ACh release is used in combination with an ACh'ase inhibitor to treat cognitive disorders, these two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of formula I capable of enhancing ACh release and an ACh'ase inhibitor in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral or parenteral dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the ACh'ase inhibitor may range from 0.001 to 100 mg/kg body weight.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art.

Example 1

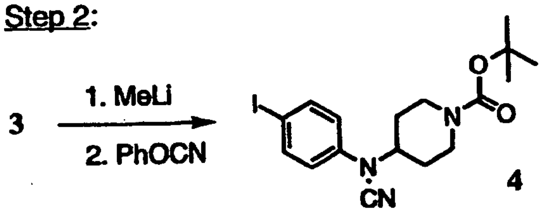
Ethyl 4-[cyano[4-[(4-methoxyphenyl)thio]phenyl]amino]-[1,4'-bipiperidine]-1'-carboxylate

Step 1:



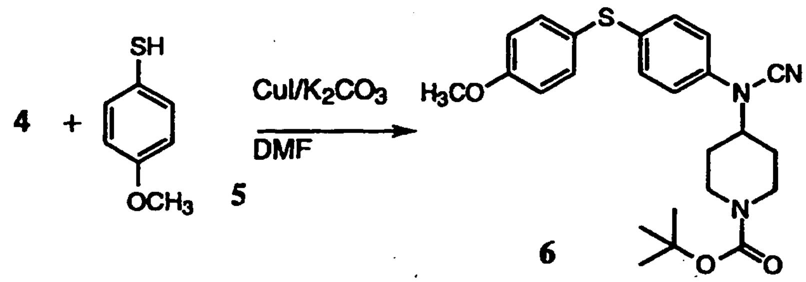
To a solution containing 4-iodoaniline **1** (8.8 g, 40.2 mmol) and N-tert-butoxycarbonyl-4-piperidone **2** (8.0 g, 40.2 mmol) in anhydrous CH_2Cl_2 (80 ml), add $Ti(O\text{-}iPr)_4$ (13.7 g, 48.2 mmol). Stir the resulting purple solution at room temperature under N_2 for 12 h. After cooling to 0°C, treat the mixture with a solution of $NaCNBH_3$ (8.3 g, 132.6 mmol) in CH_3OH (30 ml) and stir at room temperature overnight. Quench with 600 ml mixture of water/EtOAc (1:3), and then remove the insoluble substances by filtration through a bed of Celite®. Separate the organic phase, wash with brine, dry with Na_2SO_4 and remove the solvent to obtain 16.7 g of the crude product, which is chromatographed on silica gel using EtOAc/hexane (1:4) as the eluent to give 8.3 g (49%) of the product **3** as white solid.

Step 2:



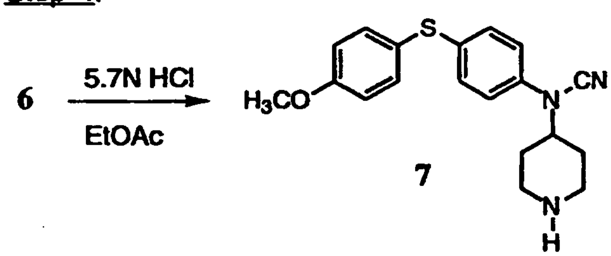
To a dry flask kept under a static pressure of N_2 add anhydrous THF (250 ml) and **3** (15.0 g, 37.0 mmol), cool to -78°C, and add 1M CH_3Li in hexane (26 ml, 37.0 mmol) at a rate such that the reaction temperature is maintained below -65C. Add phenyl cyanate (6.7 g, 56.0 mmol) at such a rate as to prevent the reaction from exotherming above -60°C and stir for 1 h. Allow the resulting solution to come to room temperature and stir overnight. Pour the reaction mixture into water and extract with EtOAc. Wash the combined extracts once with brine, dry over anhydrous Na_2SO_4, remove the solvent and flash chromatograph the residue on silica gel eluting with EtOAc:hexanes (1:4) to give 8.25 g (52%) of the product **4** as off-white solid.

Step 3:



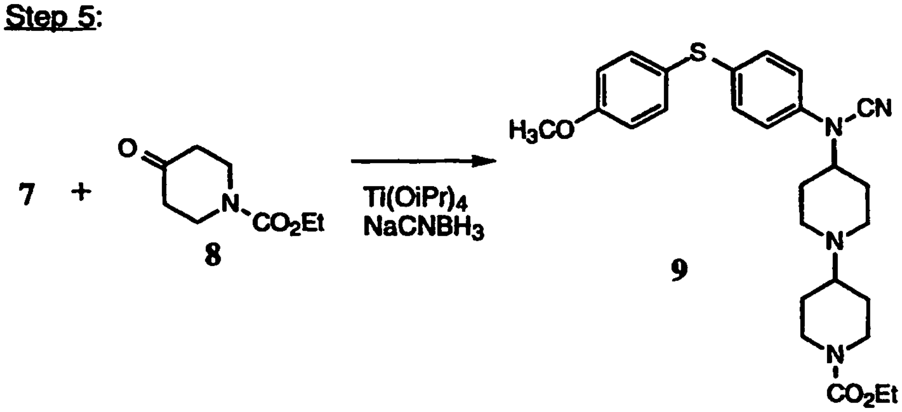
Stir a mixture of **4** (5.0g, 12.0 mmol), 4-methoxythiophenol **5** (1.96g 14.0 mmol), CuI (2.67g, 14.0 mmol), anhydrous K_2CO_3 (6.60g, 48.0 mmol) and DMF (6 ml) at 110°C for 6 h under N_2, monitoring the progress of the reaction by TLC. Cool, add water (50 ml) and benzene (50 ml) with stirring and remove the insoluble substances by filtration. Separate the organic phase, wash with brine, and dry with Na_2SO_4. Remove the solvent under reduced pressure to give a brown oil residue and purify by chromatography on silica gel, eluting with hexane/EtOAc (5:1) to give the sulfide **6** (2.6 g, 49 %) as colorless oil.

Step 4:



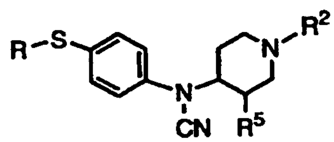
Stir a solution of **6** (2.6 g, 5.91 mmol) in EtOAc (50 ml) containing 5.7N HCl (20.5 ml) at room temperature for 4 h. Cool the reaction mixture and basify to pH 8 with a saturated solution of $NaHCO_3$. Separate the organic phase, wash with brine and dry with Na_2SO_4 to give 1.7 g (85 %) of the product **7** as yellow oil.

Step 5:

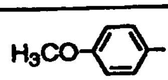
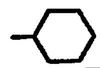
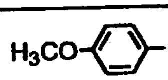
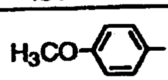
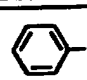
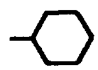
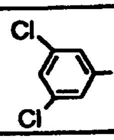
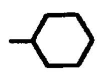
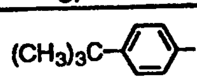
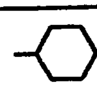
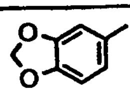
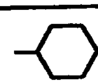
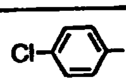
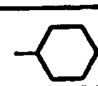
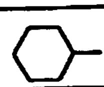
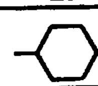


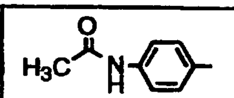
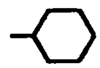
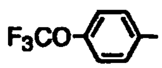
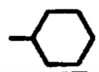
To a mixture containing 7 (1.1 g, 3.24 mmol), N-carbethoxy-4-piperidone 8 (1.66 g, 9.72 mmol) and $Ti(O\text{-}iPr)_4$ (4.61 g, 16.20 mmol), add enough dry CH_2Cl_2 (15 ml) to enable smooth stirring. Stir at room temperature under N_2 for 12 h, cool the mixture (0°C) and treat with a solution of $NaBH_3CN$ (1.0 g, 16.20 mmol) in CH_3OH (6 ml). Stir at room temperature for 12 h, and quench the reaction with 300 ml of EtOAc/water (3:1). Remove the insoluble substances by filtration through a bed of Celite®. Separate the organic phase, wash with brine and dry with Na_2SO_4. Remove the solvent to obtain a yellow oil and purify by chromatography on silica gel using EtOAc/hexane (9:1) as the eluent to give 820 mg (51 %) of 9 as sticky white solid.

Using a similar procedure, compounds of the following structure are prepared

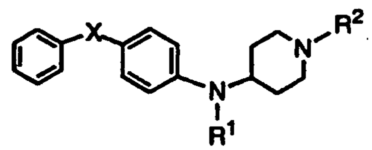


wherein the variables are as defined in the table:

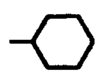
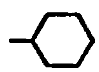
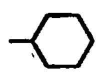
Ex.	R	R^2	R^5	HRMS calc'd	HRMS found
1A			H	422.2266	422.2258
1B	 isomer A	$-CH_2C_6H_5$	$-CH_3$	444.2110	444.2099
1C	 isomer B	$-CH_2C_6H_5$	H	444.2110	444.2108
1D			H	392.2160	392.2160
1E			H	460.1381	460.1374
1F			H	448.2786	448.2780
1G			H	436.2059	436.2052
1H			H	426.1771	426.1771
1I			H	398.2630	298.2636

1J			H	449.2375	449.2367
1K			H	476.1983	473.1987

Again using a similar procedure, compounds of the following structure are prepared

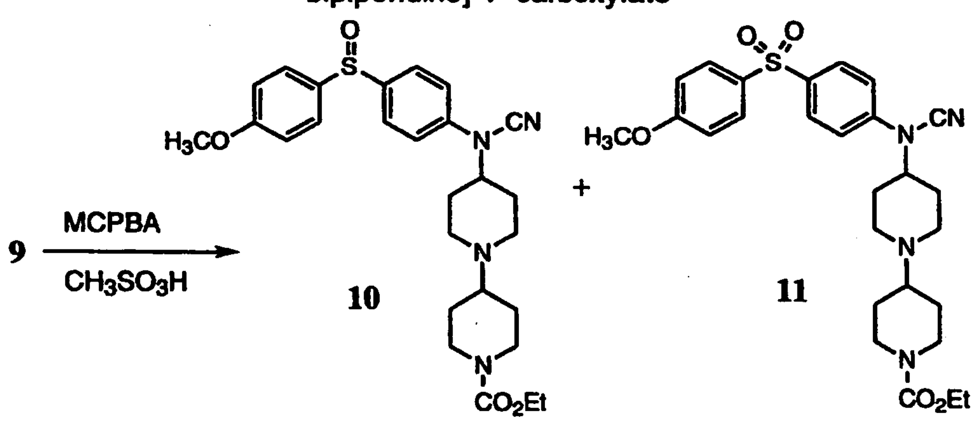


wherein the variables are as defined in the table:

Ex.	X	R1	R2	Data
1L	-O-	-CN	-C(O)OC(CH_3)3	mp=109-111°C
1M	-O-	-CN		mp=248-252°C (dec.)
1N	-CH_2O-	-CN		HRMS calc'd: 476.2008 found: 476.2010
1O	-CH_2O-	-CH_3		HRMS calc'd: 379.2749 found: 379.2748

Example 2

Ethyl 4-[cyano[4-[(4-methoxyphenyl)sulfinyl]phenyl]amino][1,4'-bipiperidine]-1'-carboxylate and Ethyl 4-[cyano[4-[(4-methoxyphenyl)sulfonyl]phenyl]amino][1,4'-bipiperidine]-1'-carboxylate

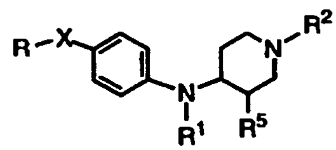


To an ice-cold solution of thioether **9** from Example 1 (750 mg, 1.52 mmol) in anhydrous CH_2Cl_2 (15 ml) containing CH_3SO_3H (9.1 ml, 4.56 mmol), add 70-75 % m-chloroperbenzoic acid (520 mg, 2.27 mmol). Stir at 0°C for 30 min, then at room temperature for 50 min, then cool the reaction mixture to 0°C and basify to pH 8 with saturated $NaHCO_3$. Separate the organic phase, wash with brine and dry with Na_2SO_4. Remove the solvent to give 730 mg of white solid. Purify by chromatography on silica gel using 2.5 % CH_3OH in CH_2Cl_2 as the eluent to give 255 mg of the sulfone **11**, followed by 305 mg of the sulfoxide **10**.

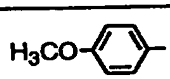
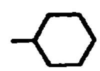
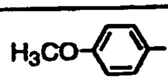
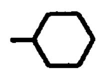
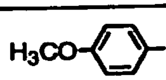
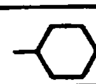
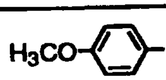
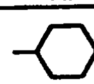
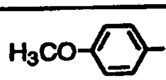
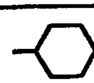
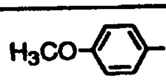
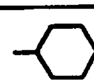
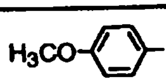
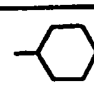
10: HRMS for $C_{27}H_{35}N_4O_4S$ calc'd: 511.2379; found 511.2381

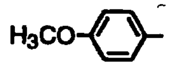
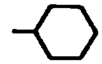
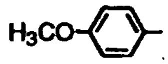
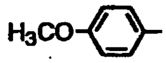
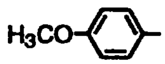
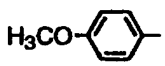
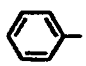
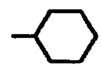
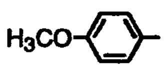
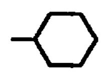
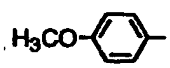
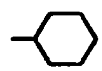
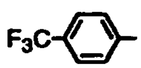
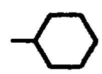
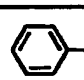
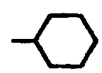
11: HRMS for $C_{27}H_{35}N_4O_5S$ calc'd: 527.2328; found 527.2324.

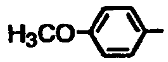
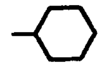
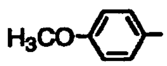
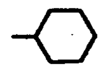
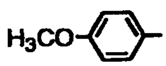
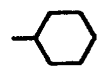
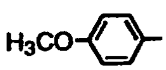
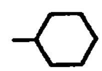
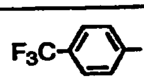
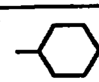
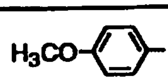
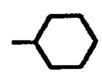
Using a similar procedure, compounds of the following structure are prepared

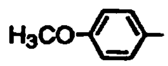
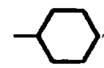
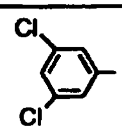
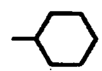
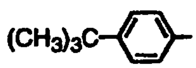
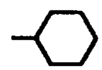
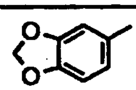
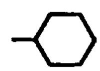
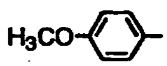
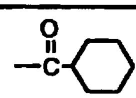
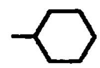
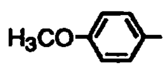
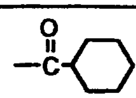
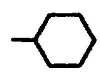
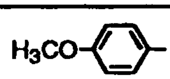
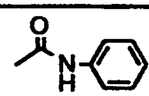
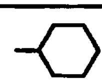
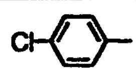
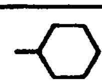
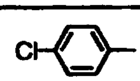
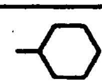
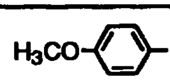
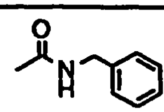
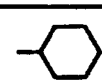
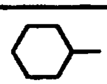
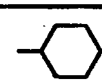


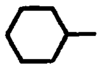
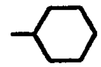
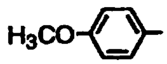
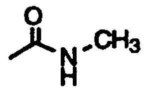
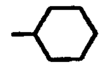
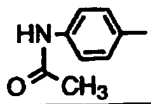
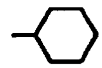
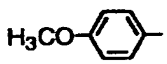
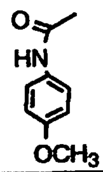
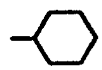
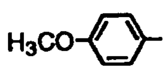
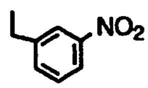
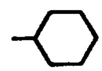
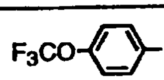
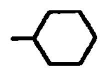
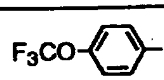
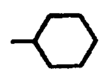
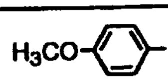
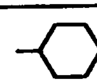
wherein the variables are as defined in the following table:

Ex.	R	X	R^1	R^2	R^5	Data
2C		$-SO_2-$	-CN		H	HRMS calc'd: 454.2164 found: 454.2150
2D		-SO-	-CN		H	HRMS calc'd: 438.2215 found: 438.2230
2E		-SO-	-CN		H	–
2F		-SO-	-CN		H	–
2G		$-SO_2-$	$-CH_3$		H	HRMS calc'd: 443.2368 found: 443.2376
2H		-SO-	$-CH_3$		H	HRMS calc'd: 427.2419 found 427.2422
2I		$-SO_2-$	$-CH_2-\underset{H}{C}=CH_2$		H	HRMS calc'd: 469.2525 found: 469.2533

2J		-SO-	$-CH_2-\underset{H}{C}=CH_2$		H	HRMS calc'd: 453.2576 found: 453.2566
2K		-SO-	-CN	$-CH_2C_6H_5$	H	HRMS calc'd: 446.1902 found: 446.1904
2L		-SO-	-CN	$-CH_2C_6H_5$	$-CH_3$	HRMS calc'd: 460.2059 found: 460.2054
2M		$-SO_2-$	-CN	$-CH_2C_6H_5$	$-CH_3$	HRMS calc'd: 476.2008 found: 476.2010
2N		-SO-	-CN	$-CH_2C_6H_5$	$-CH_3$	HRMS calc'd: 460.2059 found: 460.2050
2O		-SO-	-CN		H	HRMS calc'd: 408.2110 found: 408.2112
2P		$-SO_2-$	$-C(O)CH_2$		H	MS (CI)m+1= 471, 429, 306, 299, 225, 179, 134, 109
2Q		-SO-	$-C(O)CH_2$		H	MS (CI)m+1= 455, 439, 397, 301, 274, 225, 166, 134, 109
2R		-SO-	-CN		H	HRMS calc'd: 476.1983 found: 476.1982
2S		$-SO_2-$	-CN		H	HRMS calc'd: 424.2059 found: 424.2060

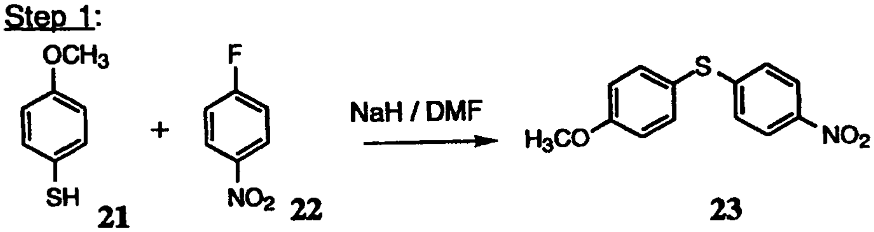
2T		$-SO_2-$	$-CH_2C_6H_5$		H	MS (FAB)m+1 =519.2, 503.2, 429.1, 367.2, 289.1, 257.1, 232.1
2U		-SO-	$-CH_2C_6H_5$		H	MS (FAB)m+1 =502.3, 488, 443, 396.2, 340.1, 320.1
2V		-SO-	$-C(O)OCH_2CH_3$		H	MS (FAB)m+1 =485.2, 469.2, 395.2, 378.2, 331.2, 320.1, 273.1, 257.1, 232.1
2W		$-SO_2-$	$-C(O)OCH_2CH_3$		H	MS (FAB)m+1 =501.2, 485.2, 419.2, 394.2, 347.2, 320.1, 274.1, 257.1, 232.1
2X		$-SO_2-$	-CN		H	HRMS calc'd: 492.1933 found: 492.1932
2Y		$-SO_2-$	$-CO(CH_2)_8CH_3$		H	MS (FAB)m+1 =583.3, 567.4, 447.4, 431.3, 413.4, 293.1, 246.1, 237.1

2Z		-SO-	$-CO(CH_2)_8CH_3$		H	MS (FAB)m+1 =567.4, 485.3, 402.3, 391.3, 347.2, 232.2, 216.3, 164.2, 137.2
2AA		$-SO_2-$	-CN		H	HRMS calc'd: 492.1279 found: 492.1282
2AB		$-SO_2-$	-CN		H	MS MH+ 480 (100%)
2AC		$-SO_2-$	-CN		H	--
2AD		$-SO_2-$			H	MS (FAB)m+1 =539.8, 523.9, 432.4, 385.2, 248.9, 234.9
2AE		-SO-			H	--
2AF		$-SO_2-$			H	--
2AG		-SO-	-CN		H	HRMS calc'd: 442.1720 found: 442.1732
2AH		$-SO_2-$	-CN		H	HRMS calc'd: 458.1669 found: 458.1667
2AI		$-SO_2-$			H	--
2AJ		-SO-	-CN		H	HRMS calc'd: 414.2579 found: 414.2583

2AK		-SO2-	-CN		H	HRMS calc'd: 430.2528 found: 430.2527
2AL		-SO2-			H	–
2AM		-SO-	-CN		H	MS MH+ 466 (100%)
2AN		-SO2-			H	–
2AO		-SO2-			H	MS (FAB)m+1 =564.2, 548.3, 463.1, 427.2, 391.3, 324.1, 310.1, 293.1
2AP		-SO-	-CN		H	HRMS calc'd: 492.1933 found: 492.1932
2AQ		-SO2-	-CN		H	HRMS calc'd: 508.1882 found: 508.1884
2AR		-SO2-	-CN		-CH3	HRMS calc'd: 468.2321 found: 468.2329

Example 3

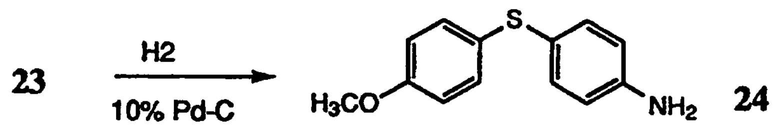
Step 1:



To an ice-cold suspension of NaH (7.1 g, 0.178 mol) in anhydrous DMF (125 ml), add 4-methoxy-benzenethiol **21** (25.0 g, 0.178 mol)

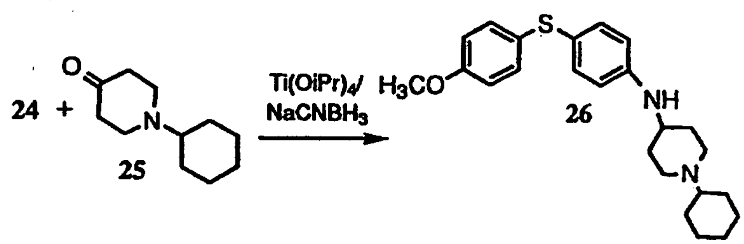
dropwise over 45 min, and stir the mixture at room temperature for 30 min. Cool the reaction mixture in an ice-bath, and treat with neat 1-fluoro-4-nitrobenzene **22** (25.2 g, 0.178 mol). Stir the resulting mixture at room temperature overnight, pour into water (1100 ml) and extract with EtOAc (3 x 500 ml). Dry the combined organic layers with Na_2SO_4 and remove the solvent to give 43 g (92%) of the product **23** as yellow crystals.

Step 2:



To a suspension of **23** (13.2 g, 50.0 mmol) in EtOH (125 ml), add 10% Pd on carbon (1.3 g) and hydrogenate the mixture at 60 psi for 12 h. Remove the catalyst by filtration through a bed of Celite® and evaporate the solvent to give 11.5 g (100%) of the product **24** as dark yellow solid.

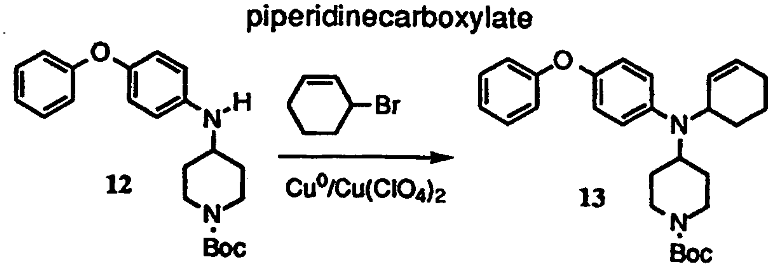
Step 3:



React aniline **24** with N-cyclohexyl-4-piperidinone derivative **25** as described in Example 1, step 1, to give substituted aniline derivative **26**.

Example 4

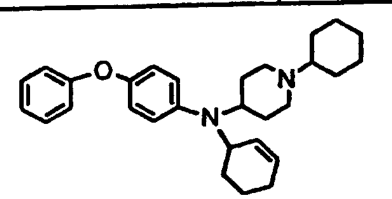
1,1-Dimethylethyl 4-[2-cyclohexen-1-yl-(4-phenoxyphenyl)amino]-1-piperidinecarboxylate



Add a mixture of amine **12** (3.0g, 8.2 mmol), prepared from 4-phenoxyaniline and N-carboethoxy-4-piperidinone using the procedures of Example, step 1, and cyclohexenyl bromide (875 mg, 5.4 mmol) in EtOAc (30 ml) to a well stirred suspension of copper (II) perchlorate hexahydrate (1.0g, 2.7 mmol) and copper metal (207 mg, 3.3 mmol) in EtOAc (15 ml) under N_2. After stirring at room temperature for 12 hours, add an aqueous solution of KCN (5.5 g in 70 ml of water). Extract the

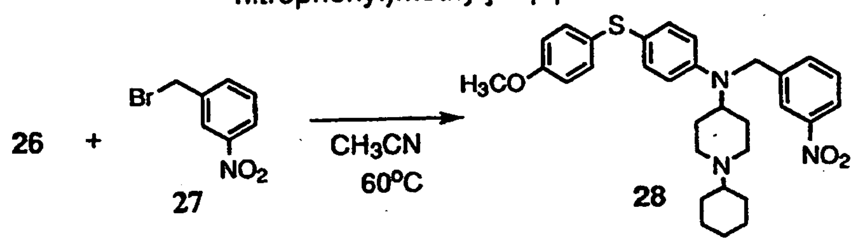
resultant clear solution with EtOAc (2 x 100 ml). Dry the combined organic extracts with Na_2SO_4 and remove the solvent by distillation. Chromatograph the residue on silica gel using EtOAc/hexane (110) as the eluent to give 1.25 g (52%) of the product **13** as semi-solid foam.

Use a similar procedure to prepare compound 4A:

4A		mp=89-92°C

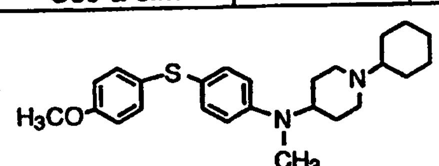
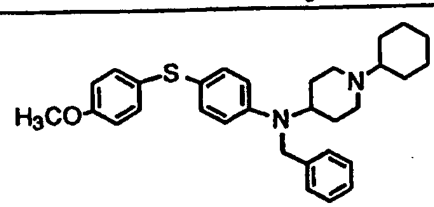
Example 5

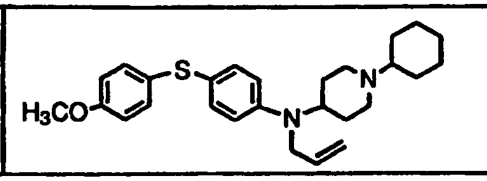
1-Cyclohexyl-N-[4-[(4-methoxyphenyl)thio]phenyl]-N-[(3-nitrophenyl)methyl]-4-piperidineamine



Dissolve aniline **26** (500 mg, 1.3 mmol) from Example 3 and 3-nitrobenzylbromide **27** (270 mg) in CH_3CN (10 ml). Heat the solution at 60°C for 3 h. After cooling to room temperature, add water (50 ml) and basify the solution with saturared aqueous K_2CO_3. Extract with CH_2Cl_2 (3x, 30mls), combine the organic extracts, dry with Na_2SO_4 and evaporate to obtain an orange oil (830 mg). Purify the crude material by chromatography using CH_2Cl_2:EtOH:NH_4OH (100:3:1) as eluant to obtain compound **28** as a yellow oil, 370mg (55%). MS (FAB)m+1=532.2, 516.2, 449.2, 369.2, 307.1, 293.1, 263.0, 215.1.

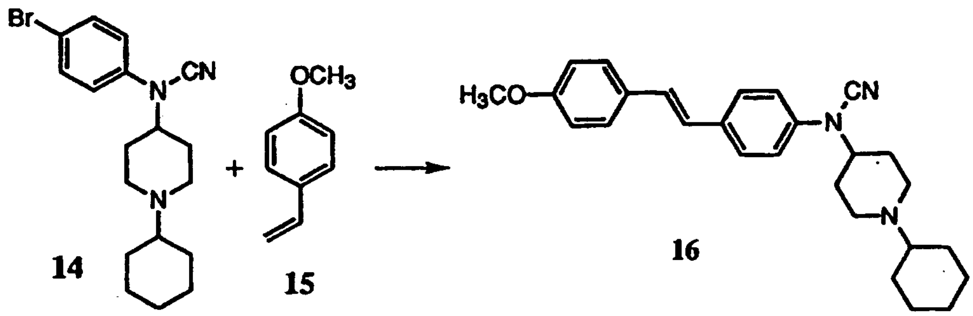
Use a similar procedure to prepare compounds 5A, 5B and 5C:

5A		HRMS for $C_{25}H_{35}N_2OS$: calc'd: 411.2470; found 411.2460
5B		MS (Cl)m+1= 439.1, 425.1, 395.1, 357.1, 332.1, 299.0, 273.0, 246.1, 212.1

5C		HRMS for $C_{27}H_{37}N_2OS$: calc'd: 437.2627; found 437.2624

Example 6

(1-Cyclohexyl-4-piperidinyl)[4-[(E)-2-(4-methoxyphenyl)-ethenyl]phenyl]cyanamide

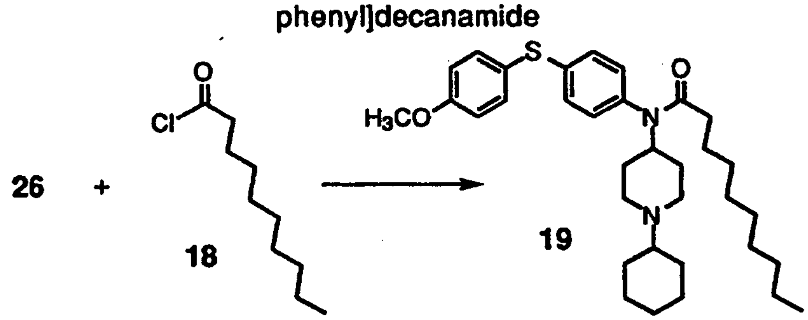


Heat a mixture of p-bromoaniline **14** (100 mg, 0.28 mmol), 4-vinylanisole **15** (479 mg, 0.37 mmol), palladium diacetate (0.64 mg, 0.003 mmol), tri-o-tolylphosphine (1.7 mg, 0.004 mmol), and dry Et_3N (0.3 ml) at 110°C for 72 h in a capped heavy-wall tube flushed with dry N_2. To the cooled mixture, add water and CH_2Cl_2. Extract the water layer with CH_2Cl_2 (2 x 10 ml), wash the combined CH_2Cl_2 solutions with water, dry over $MgSO_4$ and evaporate. Chromatograph the residue on silica gel using EtOAc/hexane (1:10) as the eluent to give the product **16** (61.1 mg, 53%) as white powder.

HRMS for $C_{27}H_{34}N_3O$: calc'd 416.2702; found 416.2688.

Example 7

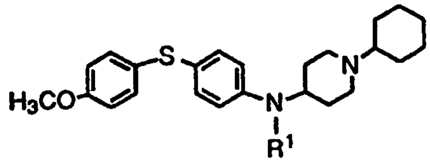
N-(1-cyclohexyl-4-piperidinyl)-N-[4-[(4-methoxyphenyl)thio]-phenyl]decanamide



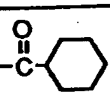
Reflux a solution of aniline **26** from Example 3 (0.67 g, 1.7 mmoles) and acid chloride **18** (0.32g, 1.7 mmoles) in CH_2Cl_2 (10 ml) for 4 to 5 hours. After cooling, add water (10 ml), then basify with solid K_2CO_3. Extract the aqueous layer with CH_2Cl_2 (2x, 10 ml). Dry the organic layer

and evaporate the solvent to obtain the crude amide. Purify by chromatography using CH_2Cl_2:EtOH:NH_4OH (100:3:1) as eluant. MS (FAB)m+1= 551.3, 395.2, 284.1, 209.2, 166.1, 122.1.

Using a similar procedure, compounds of the following structure are prepared

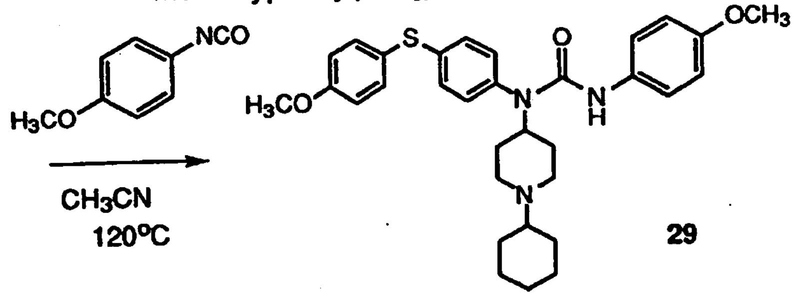


wherein R^1 is as defined in the table:

Ex.	R^1	Data
7A	-C(O)CH_3	MS (FAB) m+1= 439.1, 425.1, 395.1, 357.1, 332.1, 299.0, 273.0, 246.1, 212.1
7B	-C(O)CH_2CH_3	MS (FAB) m+1= 469.2, 386.3, 303.1, 232.1
7C		MS (FAB) m+1= 507.3, 395.2, 387.3, 304.1, 273.1, 257.1, 232.1
7D	-C(O)CH$(CH_3)_2$	MS (FAB) m+1= 467.4, 385.3, 360.3, 307.2, 257.2, 246.2, 232.1

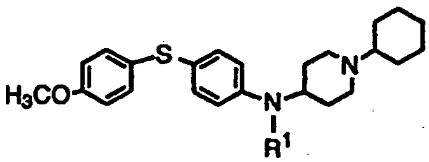
Example 8

N-(1-Cyclohexyl-4-piperidinyl)-N'-(4-methoxyphenyl)-N-[4-[(4-methoxyphenyl)thio]phenyl]urea

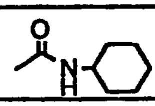
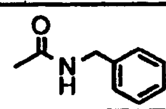
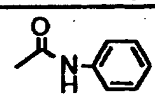
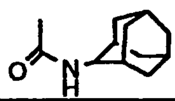


Place a solution of aniline **26** (0.33 mmoles) from Example 3 and 4-methoxy-phenylisocyanate (0.5 mmoles) in CH_3CN (1.5ml) in a sealed vial and heat in an oil bath at 120°C for 3 h. Allow the mixture to cool to room temperature and let stand overnight. Filter the resultant precipitate and wash with cold CH_3CN to give the chromatographically pure urea **29** (TLC, eluting with CH_2Cl_2:EtOH:NH_4OH (100:3:1)).

Using a similar procedure, compounds of following structure are prepared,

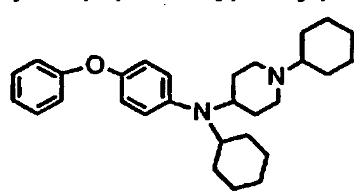


wherein the variable R^1 is as defined in the table:

Ex.	R^1	Data
8A	-C(O)NHCH$_3$	MS (FAB) m+1= 454.3, 396.2, 347.2, 289.1, 246.1, 232.1
8B		-
8C	-C(O)NHCH$_2$C(O)OCH$_2$CH$_3$	-
8D		-
8E		-
8F		-

Example 9

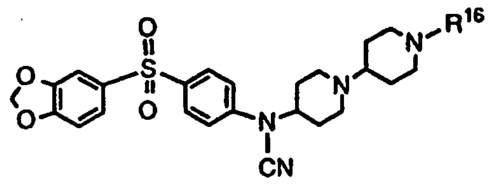
N,N'-Dicyclohexyl-N-(4-phenoxyphenyl)-4-piperidinamine



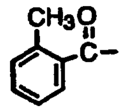
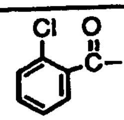
Hydrogenate a mixture of the product of Example 4A (56.9 mg, 0.13 mmol) and 10% Pd/C (8 mg) in THF (2 mL) at 1 atm pressure of H_2 for 5 h. Filter the mixture through Celite®, wash the Celite® with CH_2Cl_2 and concentrate the filtrate to obtain 54. 1 mg of the product as a colorless oil. HRMS for $C_{29}H_{41}N_2O$: calc'd: 433.3219; found 433.3212.

Examples 10A to D

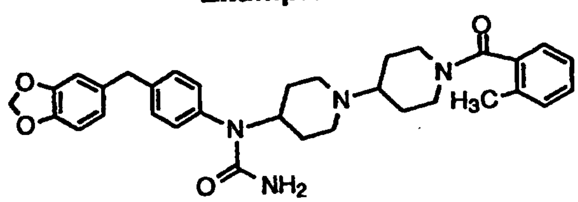
Using a procedure similar to that described in Example 1, compounds of the following formula are prepared:



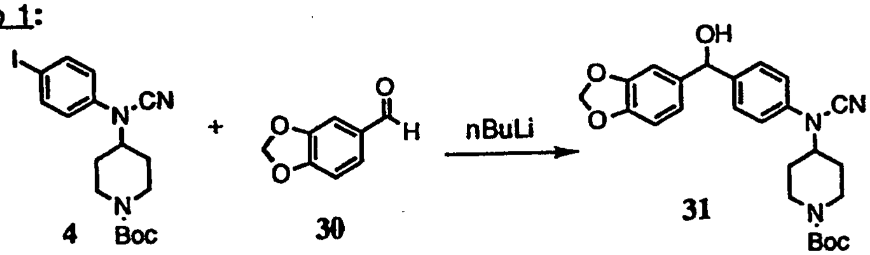
wherein the variables are as defined in the table:

Ex.	R^{18}	HRMS calc'd	HRMS found
10A		587.2328	587.2316
10B		607.1782	607.1769
10C	$CH_3CH_2SO_2$	561.1842	561.1848
10D	$CH_3(CH_2)_2SO_2$	575.1998	575.2006

Example 11

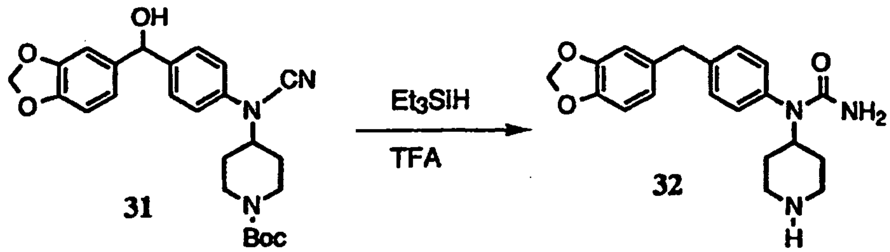


Step 1:



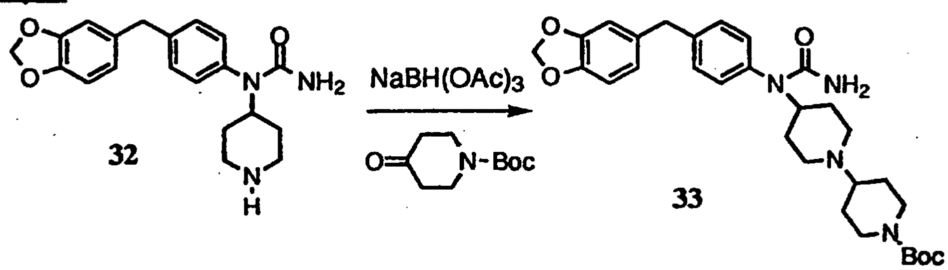
To a solution of **4** (1.0 g, 2.34 mmol) in anhydrous THF (10.0 ml) at -78°C was added n-BuLi (0.94 ml, 2.34 mmol, 2.5M hexane) . The resulting bright yellow mixture was stirred for 10 min., then was treated with a solution of piperinal **30** (281 mg, 1.87 mmol) in THF (3.0 ml). The mixture was stirred at -78°C for 1 hr, then warmed to room temperature overnight. The mixture was quenched with sat. NH_4Cl, the THF was evaporated and the aqueous residue was extracted with EtOAc (3X). The combined organic phase was washed with water and brine, dried over Na_2SO_4, filtered and the solvent was removed to obtain 1.07 g of crude product, which was chromatographed on silica gel using EtOAc/hexane (1:4) as the eluent to give 240 mg (28%) of the product **31** as a yellow solid.

Step 2:



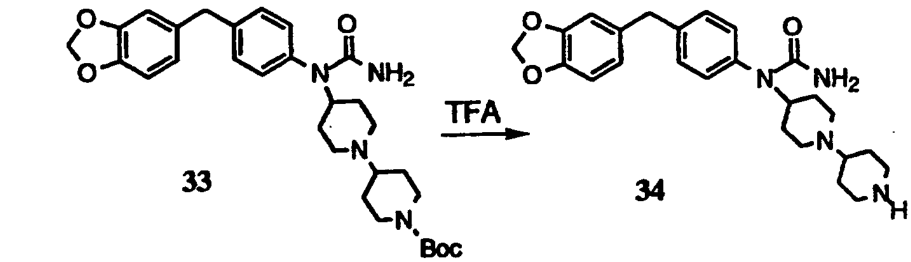
To a solution of **31** (240 mg, 0.53 mmol) in CH_2Cl_2 (10.0 ml) was added Et_3SiH (1.1g, 9.53 mmol) followed by trifluoroacetic acid (6.04 g, 53.0 mmol). The resulting yellow solution was heated at reflux 12 hrs, then cooled to room temperature. Most of the volatiles were evaporated and the residue basified to pH 8 with 1.0N NaOH. The residue was extracted with EtOAc (4X) while saturating the aqueous phase with NaCl crystals. The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give 220 mg of product **32** as a yellow oil.

Step 3:



To a solution of amine **32** (240 mg, 0.72 mmol) in CH_2Cl_2 (4.0 ml) was added a solution of N-Boc-4-piperidone (215 mg, 1.08 mmol) in CH_2Cl_2 (2.0 ml) followed by glacial acetic acid (0.16 ml, 2.88 mmol). The mixture was stirred at room temperature for 30 min, then $NaBH(OAc)_3$ (456 mg, 2.16 mmol) was added and stirring at room temperature was continued for 12 hr. The reaction mixture was diluted with EtOAc and washed with 1N NaOH (3X). The organic phase was dried over Na_2SO_4, filtered and concentrated to 620 mg of yellow solid. The crude product was flash chromatographed on silica gel, eluting with EtOH:EtOAc (20:80) to afford 115 mg (31%) of product **33** as a white solid.

Step 4:



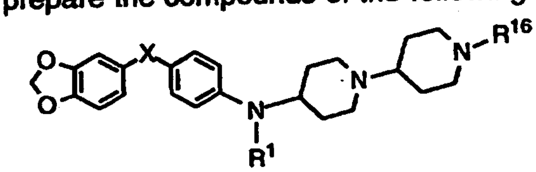
33 34

To a solution of amine **33** (110 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (2.0 ml) was added CF_3CO_2H (0.16 mmol, 2.1 mmol). The resulting mixture was stirred at room temperature for 1 hr, then quenched with water. The biphasic mixture was basified with 1N NaOH, extracted with CH_2Cl_2 (3X), the combined organic phase was dried over Na_2SO_4 and evaporated to give 59 mg (67%) of product **34** as a yellow solid.

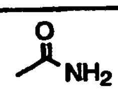
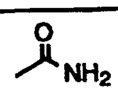
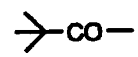
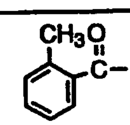
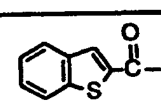
Step 5:

To a solution of amine **34** (43 mg, 0.10 mmol) in CH_2Cl_2 (1.5 ml) containing Et_3N (12.1 mg, 0.12 mmol) was added o-toluoyl chloride (18.6 mg, 0.12 mmol). The yellow mixture was stirred at room temperature for 1 hr. The crude reaction mixture was directly applied on a prep TLC plate (2000 micron) and eluted with EtOH:EtOAc (20:80) to give 25 mg (45%) of the title compound as yellow viscous oil.

Similarly, prepare the compounds of the following formula:



wherein X, R^1 and R^{16} are as defined in the following table:

Ex.	X	R^1	R^{16}	HRMS calc'd	HRMS found
11A	$-CH_2-$		H	437.2553	437.2555
11B	$-CH_2-$			537.3077	537.3090
11C	$-CH_2-$	$-CH_3$		526.3070	526.3072
11D	$-CH_2-$	$-CH_3$		568.2634	568.2634

Following are descriptions of the pharmacological test procedures.

MUSCARINIC BINDING ACTIVITY

The compound of interest is tested for its ability to inhibit binding to the cloned human m1, m2 and m4 muscarinic receptor subtypes. The sources of receptors in these studies were membranes from stably transfected CHO cell lines which were expressing each of the receptor subtypes. Following growth, the cells were pelleted and subsequently homogenized using a Polytron in 50 volumes cold 10 mM Na/K phosphate buffer, pH 7.4 (Buffer B). The homgenates were centrifuged at 40,000 x g for 20 minutes at 4°C. The resulting supernatants were discarded and the pellets were resuspended in Buffer B at a final concentration of 20 mg wet tissue/ml. These membranes were stored at -80°C until utilized in the binding assays described below.

Binding to the cloned human muscarinic receptors was performed using ^{3}H-quinuclidinyl benzilate (QNB) (Watson et al., 1986). Briefly, membranes (approximately 8, 20, and 14 µg of protein assay for the m1, m2, and m4 containing membranes, respectively) were incubated with ^{3}H-QNB (final concentration of 100-200 pM) and increasing concentrations of unlabeled drug in a final volume of 2 ml at 25°C for 90 minutes. Non-specific binding was assayed in the presence of 1 µM atropine. The incubations were terminated by vacuum filtration over GF/B glass fiber filters using a Skatron filtration apparatus and the filters were washed with cold 10mM Na/K phosphate butter, pH 7.4. Scintillation cocktail was added to the filters and the vials were incubated overnight. The bound radioligand was quantified in a liquid scintillation counter (50% efficiency). The resulting data were analyzed for IC_{50} values (i.e. the concentration of compound required to inhibit binding by 50%) using the EBDA computer program (McPherson, 1985). Affinity values (K_i) were then determined using the following formula (Cheng and Prusoff, 1973);

$$K_i = \frac{IC_{50}}{1+\left[\frac{\text{concentration of radioligand}}{\text{affinity } (K_D) \text{ of radioligand}}\right]}$$

Hence a lower value of K_i indicates greater binding affinity.

The following publications, the entire contents of which are incorporated herein by reference, explain the procedure in more detail.

Cheng, Y.-C. and Prusoff, W.H., Relationship between the inhibitory constant (K_i) and the concentration of inhibitor which causes 50

per cent inhibition (IC_{50}) of an enzymatic reaction. Biochem. Pharmacol. 22: 3099-3108, 1973.

McPherson, G.A. Kinetic, EBDA, Ligand, Lowry: A Collection of Radioligand Binding Analysis Programs. Elsevier Science Publishers BV, Amsterdam, 1985.

Watson, M.J, Roeske, W.R. and Yamamura, H.I. [^{3}H] Pirenzepine and (-)[^{3}H)quinuclidinyl benzilate binding to rat cerebral cortical and cardiac muscarinic cholinergic sites. Characterization and regulation of antagonist binding to putative muscarinic subtypes. J. Pharmacol. Exp. Ther. 237: 411-418, 1986.

To determine the degree of selectivity of a compound for binding the m2 receptor, the K_i value for m1 receptors was divided by the K_i value for m2 receptors. A higher ratio indicates a greater selectivity for binding the m2 muscarinic receptor. A similar calculation is made to determine the m4 selectivity.

MICRODIALYSIS METHODOLOGY

The following procedure is used to show that a compound functions as an m2 antagonist.

Surgery: For these studies, male Sprague-Dawley Rats (250-350 g) were anesthetized with sodium pentobarbital (54 mg/kg, ip) and placed on a Kopf sterotaxic apparatus. The skull was exposed and drilled through to the dura at a point 0.2 mm anterior and 3.0 mm lateral to the bregma. At these coordinates, a guide cannula was positioned at the outer edge of the dura through the drilled opening, lowered perpendicularly to a depth of 2.5 mm, and permanently secured with dental cement to bone screws. Following the surgery, rats were given ampicillin (40 mg/kg, ip) and individually housed in modified cages. A recovery period of approximately 3 to 7 days was allowed before the microdialysis procedure was undertaken.

Microdialysis: All of the equipment and instrumentation used to conduct in vivo microdialysis was obtained from Bioanalytical Systems, Inc. (BAS). The microdialysis procedure involved the insertion through the guide cannula of a thin, needle-like perfusable probe (CMA/12,3 mm x 0.5 mm) to a depth of 3 mm in striatum beyond the end of the guide. The probe was connected beforehand with tubing to a microinjection pump (CMA-/100). Rats were collared, tethered, and, following probe insertion, were placed in a large, clear, plexiglass bowl

with litter material and access to food and water. The probe was perfused at 2 µl/min with Ringer's buffer (NaCl 147 mM; KCl 3.0 mM; $CaCl_2$ 1.2 mM; $MgCl_2$ 1.0 mM) containing 5.5 mM glucose, 0.2 mM L-ascorbate, and 1 µM neostigmine bromide at pH 7.4). To achieve stable baseline readings, microdialysis was allowed to proceed for 90 minutes prior to the collection of fractions. Fractions (20 µl) were obtained at 10 minute intervals over a 3 hour period using a refrigerated collector (CMA/170 or 200). Four to five baseline fractions were collected, following which the drug or combination of drugs to be tested was administered to the animal. Upon completion of the collection, each rat was autopsied to determine accuracy of probe placement.

Acetylcholine (ACh) analysis: The concentration of ACh in collected samples of microdialysate was determined using HPLC/electrochemical detection. Samples were auto-injected (Waters 712 Refrigerated Sample Processor) onto a polymeric analytical HPLC column (BAS, MF-6150) and eluted with 50 mM Na_2HPO_4, pH 8.5. To prevent bacterial growth, Kathon CG reagent (0.005%) (BAS) was included in the mobile phase. Eluent from the analytical column, containing separated ACh and choline, was then immediately passed through an immobilized enzyme reactor cartridge (BAS, MF-6151) coupled to the column outlet. The reactor contained both acetylcholinesterase and choline oxidase covalently bound to a polymeric backbone. The action of these enzymes on ACh and choline resulted in stoichiometric yields of hydrogen peroxide, which was electrochemically detected using a Waters 460 detector equipped with a platinum electrode at a working potential of 500 mvolts. Data acquisition was carried out using an IBM Model 70 computer equipped with a microchannel IEEE board. Integration and quantification of peaks were accomplished using "Maxima" chromatography software (Waters Corporation). Total run time per sample was 11 minutes at a flow rate of 1 ml/min. Retention times for acetylcholine and choline were 6.5 and 7.8 minutes, respectively. To monitor and correct for possible changes in detector sensitivity during chromatography, ACh standards were included at the beginning, middle and end of each sample queue.

Increases in ACh levels are consistent with presynaptic m2 receptor antagonism.

For preferred compounds of formula I, the following values for K_i binding to m1, m2 and m4 receptors were found, and the selectivity ratios calculated:

Ex.	K_i, nM, m1	K_i, nM, m2	m2 Selectivity Ratio (K_i,m1/K_i,m2)	K_i, nM, m4	m4 Selectivity Ratio (K_i,m4/K_i,m2)
1N	667.2	40.8	16.4	66.4	1.6
2E	189.0	9.0	21.0	39.3	4.4
2G	285	15.2	18.8	50	3.3
2I	47.1	3.7	12.7	10.1	2.7
2AC	10.0	0.44	22.7	1.60	3.6
2AK	232.5	18.8	17.2	25.5	1.4
2AM	212.4	13.7	15.5	41.4	3.0

Other compounds in accordance with formula I were tested with the following ranges of results:

K_i binding to m1 receptor, nM: 2.3 to 2227 with undetermined values up to > 10000.

K_i binding to m2 receptor, nM: 0.44 to 583 with undetermined values up to > 4300.

K_i binding to m4 receptor, nM: 0.96 to 1332.5 with undetermined values up to > 3000.

Selectivity Ratios:

m2 Selectivity Ratio:

K_i for m1/K_i for m2: 0.3 to 22.7 without regard to any undetermined K_i values.

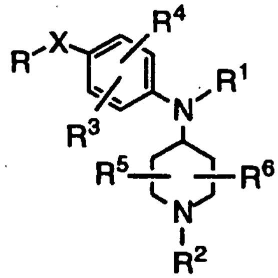
m4 Selectivity Ratio:

K_i for m4/K_i for m2: 0.3 to 6.9 without regard to any undetermined K_i values.

Compounds of formula I in combination with an ACh' ase inhibitor have an effect on ACh release. The present invention therefore also relates to administering a compound of formula I in combination with any other ACh' ase inhibitor including, but not limited to, E-2020 (available from Eisai Pharmaceutical) and heptylphysostigmine.

What is Claimed:

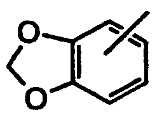
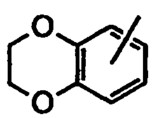
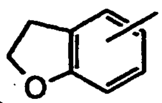
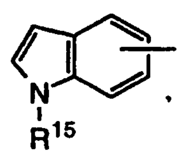
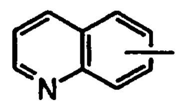
1. A compound having the structural formula

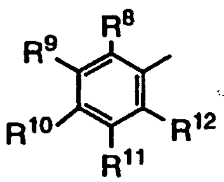
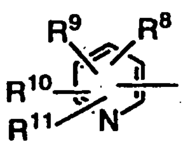


or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein

X is a bond, -O-, -S-, -SO-, $-SO_2-$, -CO-, $-C(OR^7)_2-$, $-CH_2-O-$, $-O-CH_2-$, -CH=CH-, $-CH_2-$, $-CH(C_1-C_6$ alkyl)-, $-C(C_1-C_6$ alkyl$)_2-$, $-CONR^{17}-$, $-NR^{17}CO-$, $-SO_2NR^{17}-$ or $-NR^{17}SO_2-$;

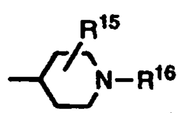
R is C_3-C_6 cycloalkyl,

 ,  ,  ,  ,  ,

 or  ;

R^1 is H, -CN, $-CF_3$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, C_3-C_6 alkenyl, $-COR^{15}$, $-COO(C_1-C_6$ alkyl), -COO(aryl), -COO(heteroaryl), $-COO((C_1-C_6$ alkyl)aryl), $-COO((C_1-C_6$ alkyl)heteroaryl), $-(C_1-C_6$ alkyl)aryl, $-(C_1-C_6$ alkyl)heteroaryl or $-CON(R^{13})_2$;

R^2 is C_3-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, t-butoxycarbonyl or

 ;

R^3 and R^4 are independently selected from the group consisting of H, halo, $-CF_3$, C_1-C_6 alkyl, C_1-C_6 alkoxy and -OH;

R^5 and R^6 are independently selected from the group consisting of H, C_1-C_6 alkyl, $-CF_3$, C_1-C_6 alkoxy, -OH, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, $R^{13}CONH-$, $R^{14}OCONH-$, $R^{13}NHCONH-$ and $NH_2CONR^{13}-$;

R^7 is independently selected from the group consisting of H and alkyl, provided that both R^7 groups are not H; or the two R^7 groups may be joined to form —$(CH_2)_p$- wherein p is an integer of 2 to 4;

R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from the group consisting of H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, benzyloxy, benzyloxy substituted by -NO_2 or -N(R^{14}), halo C_1-C_6 alkyl, polyhalo C_1-C_6 alkyl, -NO_2, -CN, -SO_2, -OH, -NH_2, -N$(R^{14})_2$, -HCO, polyhalo C_1-C_6 alkoxy, acyloxy, (C_1-C_4 alkyl)$_3$Si-, (C_1-C_6 alkyl)SO_{0-2}, arylsulfonyl, heteroaryl-sulfonyl, acyl, (C_1-C_6 alkoxy)CO-, -OCON$(R^{14})_2$, -NHCOO-(C_1-C_6)alkyl, -NHCO-(C_1-C_6 alkyl), phenyl, hydroxy(C_1-C_6 alkyl) or morpholino;

R^{13} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkyl)COOR^{15}, aryl, heteroaryl, -(C_1-C_6 alkyl)aryl, -(C_1-C_6 alkyl)heteroaryl and adamantyl;

R^{14} is independently selected from the group consisting of H and C_1-C_6 alkyl;

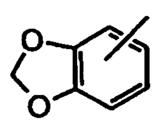
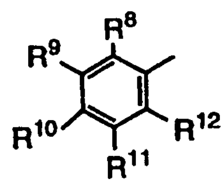
R^{15} is H, C_1-C_{20} alkyl, C_1-C_6 cycloalkyl, aryl or heteroaryl;

R^{16} is H, C_1-C_6 alkyl, -COR^{15}, C_1-C_6 alkoxycarbonyl, $(R^{14})_2$NCO- or -SO_{1-2}-R^{15}; and

R^{17} is H, C_1-C_6 alkyl, aryl or heteroaryl.

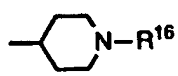
2. A compound of claim 1 wherein X is -SO- or -SO_2-.

3. A compound of any of claims 1 or 2 wherein R is

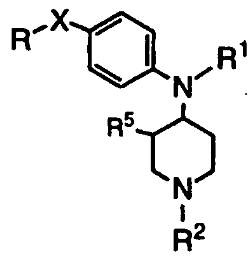
 or  .

4. A compound of any of claims 1, 2 or 3 wherein R^3 and R^4 are each hydrogen and R^5 and R^6 are independently hydrogen or methyl.

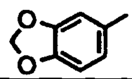
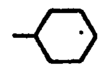
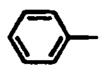
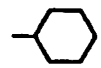
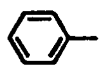
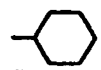
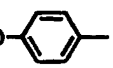
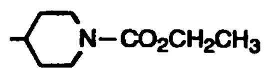
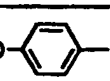
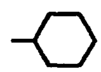
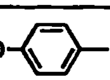
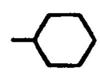
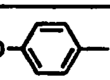
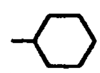
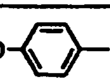
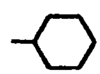
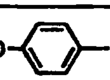
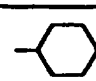
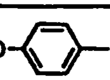
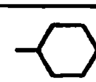
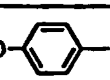
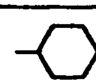
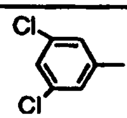
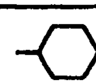
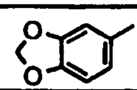
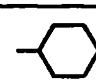
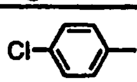
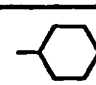
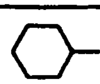
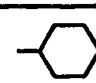
5. A compound of any of claims 1, 2, 3 or 4 wherein R^1 is cyano, C_1-C_6 alkyl or C_3-C_6 alkenyl.

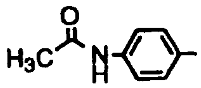
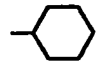
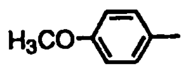
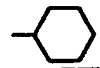
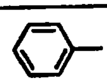
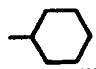
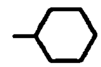
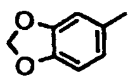
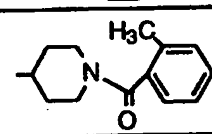
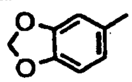
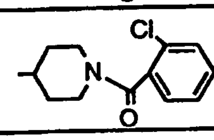
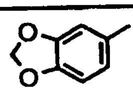
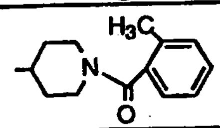
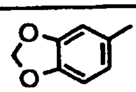
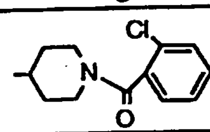
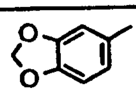
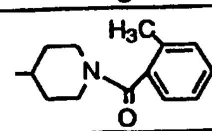
6. A compound of any of claims 1, 2, 3, 4 or 5 wherein R^2 is cyclohexyl or , wherein R^{16} is -C(O)-R^{15}.

7. A compound as defined in claim 1 selected from the group consisting of compounds represented by the formula



wherein R, X, R^1, R^2 and R^5 are as defined in the following table

R	X	R^1	R^2	R^5
	-S-	-CN		H
	-O-	-CN		H
	$-CH_2O-$	-CN		H
H_3CO-	-SO-	-CN		H
H_3CO-	$-SO_2-$	-CN		H
H_3CO-	-SO-	-CN		H
H_3CO-	$-SO_2-$	$-CH_3$		H
H_3CO-	-SO-	$-CH_3$		H
H_3CO-	$-SO_2-$	$-CH_2-CH{=}CH_2$		H
H_3CO-	-SO-	$-CH_2-CH{=}CH_2$		H
H_3CO-	$-SO_2-$	$-CH_2C_6H_5$		H
	$-SO_2-$	-CN		H
	$-SO_2-$	-CN		H
	-SO-	-CN		H
	$-SO_2-$	-CN		H

	-SO-	-CN		H
	$-SO_2-$	-CN		H
	-O-			$-CH_3$
	$-CH_2-$	-CN		H
	$-CH_2-$	-CN		H
	$-SO_2-$	-CN		H
	$-SO_2-$	-CN		H
	$-CH_2-$	$-CH_3-$		H

8. A pharmaceutical composition comprising a compound as defined in any of claims 1, 2, 3, 4, 5, 6 or 7, alone or in combination with an acetylcholinesterase inhibitor, in combination with a pharmaceutically acceptable carrier.

9. A process for the preparation of a pharmaceutical composition as defined in claim 8 comprising admixing a compound as claimed in any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor, with a pharmaceutically acceptable carrier.

10. The use of a compound of any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor, for the preparation of a medicament for treating a cognitive or neurodegenerative disease.

11. A kit for treating a cognitive or neurodegenerative disease comprising separate containers in a single package that contain pharmaceutical compounds for use in combination, wherein one container contains a compound in accordance with any of claims 1 to 7 that

enhances acetylcholine release and a separate container contains an acetylcholinesterase inhibitor, said compound and inhibitor each being in a pharmaceutically acceptable carrier and their combined quantities being an effective amount.

12. A method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of any of claims 1 to7, alone or in combination with an acetylcholinesterase inhibitor.